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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/058,835	RICHARDSON ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,36,38,40,42 and 46-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,36,38,40,42 and 46-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse in the reply filed on 25 February 2008 is acknowledged.

Specifically, applicants' elect: in response to the Office Action mailed January 25, 2008, and the requirement for an election of species therein, applicants hereby elect the species wherein the small molecule drug is a beta-adrenergic stimulator and the controlled release carrier is a polyethylene glycol group- containing macromolecule. It is believed that claims 33, 38, 40, 42, 46-51, 53-55 and 57-63 encompass the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 38, 40, 42, 46-51, 53-55 and 57-63 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, applicants disclose the limitation in claim 33, thus:

wherein said substance is a small molecule drug which is: a drug that kills fat cells; methotrexate; bromo-deoxyuridine; actinomycin D; nocodazole; brefeldin A; a beta-adrenergic stimulator; or, an alpha-2 adrenergic inhibitor.

However, the instant specification is silent in regard to any embodiments and/or teachings drawn to a specific fat cell inhibitor as disclosed in instant claim 33. In the examples of the specification, TNF is disclosed as a generic agent of choice but there is no specificity as to

which agent is indicated for treatment for the reduction of normal but undesired adipose tissue. The limitation in claim 33 is not supported in the specification via any description or explanation. The listing of these agents as appears on page 4 of the specification is not further elucidated in such a way that one of skill would know that these agents are the central issue of the claimed invention. It would not be apparent based on the embodiment cited in the specification that the inventive objective is based on theses anti-cancer agents.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 33 recites the broad recitation wherein said wherein said substance is a small molecule drug which is: a drug that kills fat cells; methotrexate; bromo-deoxyuridine; actinomycin D; nocodazole; brefeldin A; a beta-adrenergic stimulator; or, an alpha-2 adrenergic inhibitor. , etc., .Within the claim, it also recites specific drug agents which is the narrower statement of the range/limitation in comparison to the specification of certain classifications of drugs also represented such as beta-adrenergic stimulators. Specifically, the mixture of broad classifications of drug agents in association with specifically named drug agents is not proper for the purposes indefiniteness.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 33,36,38,40, 42, 46-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. (USPN 6124439),Greenway, III et al. (USPN 4,588,724), Woiszwillo et al. (USPN 5,981,719) and Neville, Jr. et al. (USPN 5, 066,490) in view of Acharya (USPN 5,686,094), Hubbell (USPN 6,129,761) and Shah (USPN 6020004).

Friedman et al. teach a method of reducing obesity. The OB polypeptide has significant value for cosmetic use, in addition to the health benefits. In particular, since the OB polypeptides of the invention, including derivatives and agonist analogs thereof, are useful for modulation of the rate and quantity of fat cell deposition in an animal, they are useful for reducing unsightly fat tissue, e.g., fat deposits in the abdomen, hips, thighs, neck, and chin that do not necessarily amount to an obese condition, but which nevertheless detract from an individual's appearance. The fat reduction effect is thought to be accomplished, in part, by a reduction in appetite, i.e., a reduction in food intake, by an increase in basal metabolism, or both. Thus, the present OB polypeptide, or its derivatives or agonist analogs, is useful for administration to a subject to effect cosmetic changes in fat tissue deposits, whether by modulating fat deposition, reducing appetite, or both (column 49, lines 23-38).

Friedman et al. teach that [s]uch pharmaceutical compositions may be for administration for **injection**, or for oral, pulmonary, nasal or other forms of administration. In general, comprehended by the invention are pharmaceutical compositions comprising effective amounts of protein or derivative products of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80),

anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of **polymeric compounds such as polylactic acid, polyglycolic acid,** etc. or into liposomes. Hyaluronic acid may also be used. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Martin, pp.1435-1712, 1990, supra, which are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form (column 43, lines 14-38).

Friedman et al. does not teach a controlled release carrier and nor does Friedman et al. teach a beta adrenergic stimulator.

However, Greenway, III et al. teach a treatment for accelerating regional weight reduction in humans, wherein an active ingredient encouraging elimination of fatty deposits, preferably a beta adrenergic stimulator or an alpha-2 adrenergic inhibitor, is selectively delivered to a regional fat deposit prior to commencing or during a general weight control program, whereby body weight is preferentially reduced in the selected area. The **beta adrenergic stimulator**, preferably isoproterenol or forskolin, or the alpha-2 adrenergic inhibitor, preferably yohimbine, or combinations thereof may be delivered by any means accomplishing specific delivery to the selected area, including injection, implantation, and topical application to the skin as in an ointment or crème (abstract only).

Greenway, III et al. teach local delivery to counteract the greater responsiveness of the fat cells in the abdomen to the lipolytic effects of beta adrenergic stimulation. Applicants have found that in vivo selective delivery and application of active ingredients to regional fat deposits

can reduce those deposits preferentially during a weight control program. Specifically, local delivery of a beta adrenergic stimulator encourages lipolysis of fat cells which normally undergo lipolysis only slowly. Local delivery of an increased concentration of an alpha-2 adrenergic inhibitor has a similar effect, for the reason that inhibition of lipolysis is blocked. Examples of known beta adrenergic stimulators include, but are not limited to, theophylline, isoproterenol, forskolin and epinephrine. Examples of known alpha-2 adrenergic inhibitors include, but are not limited to, yohimbine, rauwolscine, piperoxane, phentholamine and dihydroergotamine.

Greenway, III et al. does not teach a controlled release carrier.

However, Woiszwillo et al. teach microparticles formed by mixing a macromolecule with a polymer at a pH near the isoelectric point of the macromolecule and incubating the mixture in the presence of an energy source for a predetermined length of time. **The microparticles are composed of homogeneously distributed, intertwined macromolecule and polymer**. Each microparticle allows aqueous fluids to enter and allows solubilized macromolecule and polymer to exit the microparticle and may be formulated to provide a sustained release of macromolecule and polymer from the interior of the microparticle when placed in an appropriate aqueous medium, such as under physiological conditions. Methods of production and methods of use for research, diagnostics and therapeutics are provided (abstract only).

Woiszwillo et al. does not teach polyethylene glycol group-containing macromolecule specifically.

Woiszwillo et al. does not adequately teach the specific controlled release carrier which is administered by injection into the adipose tissue at a local area such that sustained release of the substance is effected over at least 3 days by the controlled release carrier and/or where the

controlled release carrier provides release of the substance in the local area for a period of 7 to 60 days (claim 58).

However, Neville Jr. et al. teach polyethylene glycol (PEG) [which] has been conjugated to proteins by a variety of procedures to block certain functional domains [...].**These PEG conjugates can be used to administer an enzyme protein missing from the body in order to correct an enzyme deficiency disease. PEG coupling can minimize two problems, namely, rapid clearance of the unmodified protein from the vascular system, either antibody or extra antibody mediated, and the formation of antibodies to the foreign protein.** Rapid clearance and antigenic stimulation are also problems concerning the in vivo use of immunotoxins (column 4, lines 9-22).

Neville Jr. et al. teach multiple polyethylene glycol molecules have been coupled to diphtheria toxin via crosslinker 1. Steric inhibition of toxicity to non-target cells has been achieved (2.5 logs). Studies of hydrolytic rates of release of free diphtheria toxin between pH 5.5 and 6.5 indicate that the dependency on [H+] is to a power greater than 1.

Neville Jr. et al. teach the crosslinked conjugates of the present invention may be used to prepare prodrugs, which can be used to deliver an amino-group-containing biologically active substance to selected members of a heterogeneous population of cells by exposing the cells to a complex formed by crosslinking the active substance to a cell-binding partner specific for a cell-surface receptor of the selected cells. The compound binds selectively to those cells, and the active substance is released from the complex by exposure to a pH sufficiently low to cleave the crosslinker bond between the active substance and the crosslinker.

Acharya teach controlled release delivery systems suitable for parenteral applications. A variety of sophisticated approaches such as biodegradable implants, liposomes, injectable microspheres, injectable microsponges, and "self depot" injections have been reported in the literature. In all of these types of controlled release delivery systems, there are numerous limitations. A need has existed for delivery systems which can be manufactured easily and administered parenterally using currently available administration systems. With the present invention it is possible to design a delivery system which is fluid at the time of injection but polymerizes in the body to form a hydrogel matrix, to achieve controlled release of active ingredients over a period from a ***few days to many months*** (column 2, lines 20-35).

Acharya also teach and encompass the limitation of claim 56 which is drawn to a controlled release carrier in an amount of from 01. to 20 % by weight. Acharya teach if containing a pharmaceutical agent, [it] will optionally include additional edible non-toxic ingredients as conventionally employed in medicinal dosage forms. **Thus, the compositions of the invention may optionally include one or more excipients in an amount within the range of from about 0.1% to about 99% by weight and preferably from about 1% to about 95% by weight**, such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, artificial sweeteners, and inorganic salts such as calcium carbonate. Other conventional ingredients which may optionally be present include preservatives, stabilizers, plasticizers, cosolvents, anti-adherents or silica flow conditioners or glidants, such as Syloid brand silicon dioxide as well as FD&C colors (column 6, lines 48-61).

Hubell teach the carrier as a solution and as a gel. Slowly polymerizing, biocompatible, biodegradable hydrogels are provided which are useful for delivering large numbers of isolated

cells into a patient to create an organ equivalent or tissue such as cartilage. The **gels** promote engraftment and provide three dimensional templates for new cell growth. The resulting tissue is similar in composition and histology to naturally occurring tissue. In one embodiment, **cells are suspended in a polymer solution and injected directly into a site in a patient**, where the polymer crosslinks to form a hydrogel matrix having cells dispersed therein which can be implanted into a patient. Ultimately, the hydrogel degrades, leaving only the resulting tissue (column 5, lines 7-22).

Polymeric materials which are capable of forming a hydrogel are utilized. The polymer is mixed with cells for implantation into the body and is permitted to crosslink to form a hydrogel matrix containing the cells either before or after implantation in the body. In one embodiment, the polymer forms a hydrogel within the body upon contact with a crosslinking agent. A hydrogel is defined as a substance formed when an organic polymer (natural or synthetic) is crosslinked via covalent, ionic, or hydrogen bonds to create a three-dimensional open-lattice structure **which entraps water molecules to form a gel.** Naturally occurring and synthetic hydrogel forming polymers, polymer mixtures and copolymers may be utilized as hydrogel precursor links to form a hydrogel (column 7, lines 31-43).

Hubell or any of the references supra do not teach wherein a first substance released is an anti-angiogenic compound which hinders the blood supply to adipose tissue and a second substance is released later in time which induces apoptosis in adipose tissue according to instant claim 49.

However, Shah teaches the methodology and technical embodiments drawn to phase separation techniques. The present invention relates to improved methods of making polymeric

microparticles containing a variety of active ingredients, e.g. protein drugs. In addition, the present invention relates to using the above active protein containing polymeric microparticles to prepare compositions for the sustained delivery of the therapeutics (abstract only).

Shah further teaches that the release characteristics for the active ingredient from microparticles prepared by methods such as those described above may be continuous or discontinuous, and in some cases, the initial level of active ingredient release is too high or too low. Thus, various additives are often utilized in an attempt to control the release of active ingredient (column 2, lines 26-31).

Thus, the significant advantages of the present processes as compared to the processes described in the art, include for example, 1) ease of manufacture of the active ingredient loaded microparticles; 2) versatility as relates to the class of polymers and/or active ingredients which may be utilized; 3) higher yields and loading efficiencies; and 4) the provision of sustained release formulations that release active, intact active ingredient in vivo, thus providing for controlled release of active ingredient over an extended period of time (e.g. up to 180 days). As used herein the phrase "contained within" denotes a method for formulating an active ingredient into a composition useful for controlled release, over an extended period of time of the active ingredient.

Further, Shah et al. teach in the sustained-release compositions of the present invention, an effective amount of active ingredient will be utilized. As used herein, sustained release refers to the gradual release of active ingredient from the polymer matrix, over an extended period of time. The sustained release can be continuous or discontinuous, linear or non-linear, and this can

be accomplished using one or more polymer compositions, drug loadings, selection of excipients (column 7, lines 8-29).

Thus, it would have been prima facie obvious to one of skill at the time of invention to at once recognize with a reasonable expectation of success the inventive objective of the claimed invention based on the incorporating together and/or combining the references of Friedman et al. (USPN 6124439) and Greenway, III et al. (USPN 4,588,724) and Woiszwillo et al. (USPN 5,981,719) in view of Acharya (USPN 5,686,094), Hubbell (USPN 6,129,761) and Shah (USPN 6020004).

The differences in the prior art and the claims at issue are of no consequence in this instance because each and every reference, based on the same or similar subject matter, resolves the deficiencies of the other by adequately addressing each and every limitation presented by the instant claims. The references *supra* are replete with embodiments which adequately support and suggest the inventive objective of the present invention. Particularly, Neville Jr, et al. provides the essential motivation to formulate an injectable comprised of PEG because it is a hall-mark pharmaceutical carrier used in a myriad of injectable formulation because of its specific properties and characteristics which make the active agent more bioavailable. Acharya provides an encompassing motivation based on subject matter drawn specifically to ranges of formulation percentage dosing which make the range limitations of instant claim 56 obvious. The related subject matter, methods, processes and such modifications shared by all references *supra* in comparison to the inventive objective and central issue of the claimed invention is *prima facie* obvious. The skilled artisan would at once recognize with a reasonable expectation of success that this claimed invention could reasonably be deemed obvious based on the related and

overlapping subject matter of Friedman et al. (USPN 6124439) and Greenway, III et al. (USPN 4,588,724) and Woiszwillo et al. (USPN 5,981,719) in view of Acharya (USPN 5,686,094), Hubbell (USPN 6,129,761) and Shah (USPN 6020004).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB